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INTER-OFFICE CORRESPONDENCE

To:	Richard CARCHMAN	Date:	January 9, 1995
From:	Helmut Reif	Copies:	
Subject:	Comments on the usage of cotinine as a biomarker. Letter from David L. Katz, Arnold & Porter dated Dec. 14, 1994, with scientific articles attached.		

It should be tried in this comment to (a) answer as much questions as possible put forward under para (2) of the accompanying letter from Arnold & Porter and (b) to give additional thoughts and comments as have arisen during the lecture of the attached articles.

Is plasma cotinine a reliable, validated method to measure nicotine intake ?

Different to the widely accepted belief that the intake of a certain substance causes a certain fixed concentration level of that substance in body fluids the cotinine levels found are time-dependent differential concentrations which result from the supposition of intake and excretion curves. Both curves are dependent on nearly every parameter in an individual's life (smoking regime, body mass index, genetic inheritance of metabolic speed).

These facts are acknowledged in some of the attached papers by expressions such as "*Blood levels of cotinine in chronic tobacco users are fairly constant over time.*", or "*The cotinine $t_{0.5}$ is approximately 20h*". As stated in one of the papers (Zeidenberg et al., Comprehensive Psychiatry 18, 1, 93 [1977]), "*53% of the variance in cotinine levels is associated with the variance of the nicotine in cigarettes smoked per day. The remaining 47% of variance unaccounted for in these computations probably result from the individual difference factors...*".

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A real interesting question concerns the excretion kinetics of cotinine. In all scientific articles a cotinine elimination half-life [$t_{0.5}$=ln2/k] is derived, but nobody has ever checked whether the kinetics follow a first-order mechanism (which is the prime condition for application of this formula). Any other mechanism would have a concentration term in the denominator of the formula for the elimination half-life which automatically increases the half-life with decreasing concentration! Of course, there is no idea that a complicated reaction such as an enzymatic oxidation is of "molecular first-order" meaning that only one molecule takes part in the reaction. However, physicochemistry sometimes uses an approximation called "pseudo first-order" which means that

(a) the decisive reaction takes place in one step, and

(b) all other reaction partners are so abundant that one would not see any changes in concentration in the course of the reaction.

Any assumption of migration of nicotine into deeper body compartments and subsequent release from there means that the concentration of nicotine at the place where the oxidation to cotinine takes place is determined by other processes which for sure are not of first order. Therefore, the conclusion must be that

(a) one cannot calculate a half-life time of the above-mentioned form, and

(b) the influence of the individual's body set-up, life conditions, etc. are determining the cotinine concentration and excretion patterns to such an extent as to prohibit any meaningful correlation to any exposure.

These conclusions show that neither the individual excretion curve can be generalised nor generalised findings can be used for the individual.

It is self-understanding that a hypothetical, extremely detailed study of all life parameters of a single individual would render the possibility to predict the "cotinine level" of this and only this individual with a certain precision.

Do models other than "addiction" better explain smoking behaviour ?

The expression "addiction" has been greatly overused and even abused in the past years. If one follows one of the recent definitions that anything which reaches the brain and is "psychoactive" constitutes "addictive" properties then even eating should be labeled as addictive as blood sugar exerts a vital influence on the brain. As it is always in life, the extremes meet: if one wants to explain everything with one word, nothing is explained by it.

The failure of nicotine replacements in smoking cessation programs shows that one cannot single out one parameter of a habit and try to replace that

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habit by it. If this were true then astronaut feeding would be equivalent to a French dinner. The real inter-relationship of nicotine uptake and the other parameters of smoking are so intricate that none of them can be singled out. It remains to be clarified if authorities which have a clear opinion of the addictiveness of a substance can promote the same substance as a remedy against the addiction caused by it. Or should only the pleasure be killed ?

A competitive model to replace the addiction model would be that of a pleasurable habit which becomes more and more engraved into one's day-to-day life because of its multi-dimensional rewarding effects: aromatic taste, relaxation, increase of attentiveness, social contacts ("have a smoke together", "may I offer you a cigarette"), improvement in coping with daily stress, highlighting a break, oral satisfaction, or structuring a dull day.

Does nicotine replacement reliably reflect smoking behaviour and/or cravings for nicotine ?

A clear-cut "no" for the first part, a "definite may-be" for the second. As was explained earlier on, nothing can reflect smoking behaviour than smoking behaviour itself, the chewing of a pill or a gum cannot reflect the inhalation of aromatic smoke. A pleasurable habit, as it is - signaling joy of life - cannot be "replaced" by the intake of a medicament - signalling illness. A nicotine pill or chewing gum cannot be lit and rolled between the fingers, it does not release nice aroma. A nicotine spray does not cause nice clouds of smoke...

Apart from the psychological part of smoking is the release of nicotine from a cigarette and its uptake a rather short event (a "bolus") whereas the pills and gums render a constant nicotine level. If one is constantly saturated one has no incentive to go out for eating !

"Craving for nicotine" does not show with the pleasurable smoker, it is rather an indication that the previous tobacco consumption has been serving other needs than sheer smoking pleasure. A similar conclusion is valid for alcohol: if one drinks for the taste of gin-tonic, that's pleasure. If one drinks to forget the troubles of the day then it is abuse and the situation will tend towards an addiction.

"Craving" is as badly defined as "addiction" and one may find craving situations in all life habits, such as craving for food, love, etc. All habits leave an emptiness behind when stopped immediately.

Are specific nicotine levels associated with addictive-type behaviours or effects ?

It becomes more and more clear with all nicotine replacements that if there was is not a decisive will for cessation these "little helpers" do not lead to any success. This means that the substance nicotine is by no means associated

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with either an addictive or a non-addictive-type behaviour. It means rather that "addiction" is a decision (or a lack of decision) made by a person's free will. It is a blatant exaggeration to ascribe an "addictive power" to a non-living chemical substance. Is it not rather that addiction is created within a person's brain and by that person alone ?

As far as the aroma of tobacco products is concerned, nicotine adds significantly to the whole taste of smoke by its dark, brown, sometimes scratchy, sometimes mellow, and generally speaking "tobacco-like" taste. Different to wine where alcohol does not contribute very much to the bouquet, nicotine is a main player in the "tobacco bouquet". Any excessive lowering of the nicotine level could weaken the pleasure of smoking to such an extent that people do not smoke any longer. This low nicotine content could then be taken for the "decisive threshold" below which smoking is no longer "addictive". This would be as wrong a conclusion as found nowadays galore in so-called statistical meat-evaluations. The truth would be these low-level cigarettes are just tasteless and do not render any pleasure.

Is there any known correlation between plasma cotinine levels and central nervous system nicotine or cotinine levels ?

This question pertains to the "psycho activity" of nicotine. It is self-understanding that anything which we take up and what is transported by body liquids may eventually reach the central nervous system. It is further well-known that nicotine has some positive influence on the central nervous system (increase of attentiveness, later onset of Alzheimer's and Parkinson's disease).

If one were tempted to resolve that question scientifically one had to ask about the "model" at first. Are human beings all equal ? If so, are all brains equal (reactivity, threshold for triggering nervous reactions) ? For sure not. The fact that nearly everybody comes across tobacco during his life but only part of the population finds this habit pleasurable and takes it up shows that difference. Some feel better with a smoke, some not. The conclusion is that there is for sure a correlation between plasma levels and central nervous system levels, but it is individually highly different and possibly accountable for the pleasure some of us find in smoking.

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